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Do N3 Fatty Acid Supplements Effect Depressive Symptoms Post Cardiovascular Event in Men and Women Ages 40 and Older?

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Do n-3 fatty acid supplements effect depressive symptoms post cardiovascular event in men and women ages 40 and older?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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OBJECTIVE: The objective of this selective EBM review is to determine whether or not n-3 fatty acids have an effect on depressive symptoms post cardiovascular event in men and women ages 40 and older.
Study design: Systematic review of three English language random controlled trials published between 2011-2012.

DATA SOURCES: Two randomized controlled trials published after 2011 comparing the effects of n-3 fatty acid supplementation on depressive symptoms post cardiovascular event and one randomized controlled trial comparing n-3 fatty acid supplementation effects on depressive symptoms in elderly patients with diagnosed depression. The studies were obtained using the PubMed database.

OUTCOMES MEASURED: Depressive symptoms, assessed using the Geriatric Depression Scale, was the primary outcome measured in all three studies. In all studies patients depressive symptoms were measured with the GDS-15 before the trial of supplementation vs. placebo began, and then after the trial was over. Results were then compared before and after supplementation.

RESULTS: The results of these studies show an insignificant decrease in depressive symptoms of patients supplemented with n-3 fatty acids post cardiovascular event vs. a placebo. However, one study showed the potential for n-3 fatty acid supplementation in depressed elderly patients unrelated to cardiovascular events with a decrease in depressive symptoms after supplementation.[6] One subgroup in the study by Andreeva and colleagues reported an increase in depressive symptoms in men who were supplemented n-3 fatty acids for the trial.[4]

CONCLUSIONS: Based on these studies, the use of n-3 fatty acids for decreasing depressive symptoms in post-cardiovascular events can not be justified. Andreeva and colleagues, as well as Giltay and colleagues, both showed no significant difference in depressive symptoms in patients post-cardiovascular event supplemented with n-3 fatty acids assessed by the GDS-15.[4,5] However, Tajalizadekhoob et al. showed n-3 fatty acid supplementation in elderly patients with diagnosed depression does in fact improve their depressive symptoms with a NNT of 8. [6] Although the total patient number of this study was small, further investigation should continue as this proves there is lead way for the use of n-3 fatty acids for their effect in depression.

Key Words: Post-cardiovascular event, Depression, Omega-3 Fatty Acids

INTRODUCTION

Cardiovascular disease is a serious and common medical condition associated with a wide range of symptoms including chest pain, diaphoresis, and nausea. Cardiovascular events can be categorized into NSTEMI/Unstable angina and STEMI. Both are caused by narrowing or occlusion in the coronary artery system that leads to decreased perfusion to the myocardium. Ultimately the decreased perfusion results in ischemia which can be fatal.[1] Recent studies have shown a number of patients who have experienced a cardiovascular event, described above, have an increase in depression following. This paper evaluates randomized controlled trials comparing the efficacy of fatty acid supplementation on depressive symptoms in patients >40 years old who have experienced a cardiac event.

This topic is relevant to both patients and the PA practice due to its commonality. Heart disease is a major cause of disability and the leading cause of death in the United states for both men and women. Each year around 715,000 Americans have a heart attack. Of these Americans, the incidence of first heart attacks include 525,000 and the incidence of second heart attacks includes 190,000. The morbidity of heart disease counts for 26.5 million people of noninstitutionalized adults. This makes up about 11.5% of all noninstitutionalized adults in the US today.[2]

The most common type of heart disease is coronary heart disease. The total cost of this disease alone is around 108.9 billion dollars per year in the United States. This cost includes health care services, medication and lost productivity. The American Heart Association published an article in 2011 that projected future costs for cardiovascular disease to be 444 billion dollars. With strokes, heart disease is the most costly health problem our nation faces today.[2] Each year the number of visits to physician offices with

heart disease as a primary diagnosis includes 12.4 million people, this excludes ischemic heart disease. The number of patients discharged from inpatient facilities with heart disease as first-list diagnosis is around 3.7 million.[2]

The exact incidence of patients with heart disease who experience depressive symptoms after a cardiac event is unknown. Studies have shown up to 33 percent of heart attack patients develop some degree of depression. Depression not only is a psychological problem, but can also lead to worsening physical problems. Patients with depression are less likely to take care of their physical health and cut back on rehab and/or medication.[3]

Cardiovascular disease treatment involves decreasing risk factors that may cause an event such as HTN, Hyperlipidemia, Hypercholesterolemia, and Obesity. This usually begins with lifestyle changes including a low-fat, low-sodium diet, 30-minutes of moderate exercise most week days, smoking cessation and limited alcohol intake. Additional treatment modalities include a long line of medications used to treat specific risk factors including anti-hypertensive medications: diuretics, ACE-inhibitors or beta-blockers; blood thinners: Aspirin, warfarin, heparin, tPA; and cholesterol-lowering medications: statins or fibrates. Medical procedures are used in severe life threatening situations including coronary angioplasty, coronary artery bypass grafting (CABG) and heart transplant.[1]

As stated previously, recent studies have shown a link to depressive symptoms and post-cardiac events. All methods above used to treat cardiovascular disease focus solely on the physical symptoms these patients experience and disregard any psychological associations. It is proposed that n-3 fatty acid supplementation may be

used to prevent or decrease depressive symptoms in patients who have previously experienced a cardiac event.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not n-3 fatty acid supplements effect depressive symptoms post-cardiovascular event in men and women ages 40 and older.

METHODS

Criteria used for selection of studies included patients greater than 40 years old who had experienced a cardiovascular event and an intervention of n-3 fatty acid supplementation. This population was compared to an experimental group who received a visually matched placebo. Criteria used for selection of a third study included elderly patients with diagnosed depression and an intervention of n-3 fatty acid supplementation. The outcomes measured in all studies were the patients depressive symptoms. The types of studies included three randomized, double blind, placebo controlled clinical trials.

All articles were published in English in peer reviewed journals and searched for using key words such as post-cardiovascular event, depressive symptoms and n-3 fatty acids. The three studies in this review were searched using PubMed and selected by relevance to the question at hand and standards set forth by the syllabus (POEMs). Inclusion criteria for the data sources were randomized, controlled and double blinded studies. Exclusion criteria in all studies were patients under the age of 40 years old. Statistics used by the studies included adjusted OR, standardized means, RRR, ARR, NNT and p-values. The specific studies demographics and characteristics can be found in Table 1.

Table 1: Demographics and Characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Andreeva[4] (2012)	Double blind RCT	1,133	45-85	Previous MI, Unstable angina, or Ischemic stroke within 12 preceding mo of RCT	Previous cardiovascular pathology (eg. solid cancer or leukemia) and with expected survival <5 yrs	126	Long-chain n-3 PUFAs supplementation (600mg EPA and DHA in a 2:1 ratio)
Giltay[5] (2011)	Double blind RCT	2037	60-80	Previous MI within 10 years before the study	MI >10 years ago, age <60	367	n-3 fatty acid supplementation (400mg margarine spread EPA-DHA/day)
Tajaliza-dekhoob[6] (2011)	Double blind RCT	66	≥ 65	Age ≥ 65, no hx of end-stage diseases or unstable medical condition, no hx of seafood allergies, no consumption of fish oil or omega-3 supplementation 3 mo prior to participation, no hx of psychiatric d/o with exception of depression or anxiety, no dx of mental retardation	Hx of dementia reported based on their KCF profiles or MMSE of ≥ 22, individuals with GDS-15 scores >11 indicating severe depression	0	1 g of fish oil capsule/day (cod liver oil, glycerol, water and fish oil: comprised of 180mg EPA and 120mg of DHA)

OUTCOMES MEASURED

The outcomes measured in this review were depressive symptoms. Two studies measured this in patients >40 who experienced a cardiovascular event given n-3 fatty

acid supplementation versus a placebo. Another study measured depressive symptoms in diagnosed depressed elderly patients who were given n-3 fatty acid supplementation versus a placebo. Depressive symptoms were measured using the Geriatric Depression Scale (GDS-15) in all three studies.[4,5,6]

RESULTS

This review includes two randomized controlled trials comparing n-3 fatty acid supplementation effects on depressive symptoms in post-cardiovascular event patients. A third randomized controlled trial looks at the effect of n-3 fatty acid supplementation on depressive symptoms in elderly patients with diagnosed mild-moderate depression. All studies were double-blinded, included visually matched placebo's and performed on patients over the age of 40.

In the paper by Andreeva and colleagues, n-3 PUFAs were supplemented in cardiovascular disease survivors to determine their effect on depressive symptoms. Patients excluded were those with previous cardiovascular pathology and those with expected survival <5 years to maximize the results by eliminating possible confounding factors. Supplements were given in 2 capsules of 600mg EPA/DHA in a 2:1 ratio, to take once daily for 1 year and patients were then re-examined/resupplied at annual follow ups. The presence of depressive symptoms were assessed using the GDS-30. For primary analysis, scores $\leq$10 were normal and >10 were considered to have depressive symptoms. Scores were obtained after a median follow up of 4.7 $\pm$ 1.9 years. In the full sample there was no effect of n-3 PUFAs on depressive symptoms. This is shown by using results of the principal factorial logistic regression models, an adjusted OR value of 1.16 with 95% CI: 0.95, 1.141. However, when looking at men and women separately, men showed a

positive association between n-3 PUFAs and mild depressive symptoms (adjusted OR of 1.28 with a 95% CI: 1.03, 1.61). A 28% higher risk of having depressive symptoms was shown with men who received n-3 PUFA compared with those who did not. A sensitivity analysis was also performed to wean out individuals who reported use of antidepressants at baseline (50 women, 73 men). After the factorial logistic regression models were refit with the remaining participants (n=1877) the associations for n-3 PUFAs and depressive symptoms remained non-significant.[4]

Giltay and colleagues used the "Alpha Omega Trial" for their study where patients post-MI were given n-3 fatty acids (400mg margarine spread of EPA-DHA/day) versus a matched placebo. Those supplemented with EPA-DHA and placebo did not differ in baseline characteristics. Patients who had a MI over 10 years ago were excluded from the study to reinforce the association between the event itself and depressive symptoms, rather than possible confounding factors after the event had occurred. Patients less than 60 years of age were also excluded. To assess depressive symptoms of the patients the GDS-15 was used, a "yes or no" self-administered questionnaire. Completion of the questionnaires were done by trained research nurses at home or in the hospital or were mailed to the patients and self-completed. The scores ranged from 0-15 where higher scores indicate more severe depressive symptoms ($\geq$ 5: moderate-severe, >10: severe). Changes over time in depression from 40 months compared with baseline were analyzed using ANCOVA. All tests were 2-tailed and a p-value <0.05 denoted significance. At the 40 month follow up depressive symptoms did not differ from baseline between the supplemented and placebo groups. The standardized mean differences in depressive symptoms for EPA-DHA compared with placebo were -0.048 $\pm$

0.044 with a p value of 0.28. However, analysis of a small subgroup of 35 patients who used antidepressants at baseline showed a beneficial effect with n-3 fatty acid supplementation (P=0.04; Table 2).[5]

Table 2: Sub-group Analysis of Outcomes in Post-cardiovascular Event Patients Supplemented with EPA-DHA by Giltay and colleagues.

Group	Mean difference for EPA-DHA vs. Placebo	P-value
All participants (EPA-DHA n= 1007, placebo n=1030)	-0.048 $\pm$ 0.044	0.28
Antidepressant use at baseline (Antidepressant n=36, placebo n=1030)	-0.477$\pm$ 0.235	0.04

In the study by Tajalizadekhoob et al, elderly patients with mild-moderate depression were supplemented with 1 gram fish oil capsule (180mg EPA, 120mg DHA) per day to determine its effect on their depressive symptoms. Patients included those with mild to moderate depression who scored a 5-11 on the GDS-15. Those with a history of dementia and/or severe depression graded by a GDS-15 score >11 were excluded. Depression was scored before and after supplementation for 6 months using the GDS-15 administered by a clinical psychologist who was blind to the drug groups of the participants. A $\geq$ 25% decrease in GDS-15 score was considered an improvement in depression. At the end of the study there was some efficacy in the treatment of mild to moderate depression in elderly patients with n-3 FA supplementation. Patients in the fish oil group showed a greater decrease in GDS-15 scores at the end of the study. In the fish oil group 40.7% showed improvement ($\geq$25% decrease in GDS score) versus 27.6% in

the placebo group with a p-value of 0.13. The NNT was 8, therefore one of every 8 patients will have a decrease in depressive symptoms when supplemented with n-3 FA.[6]

Table 3: **Analysis of Outcomes and NNT in Patients Supplemented with n-3 FA for Improvement in Depression by Tajalizadekhoob et al.**

Number of patients	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
66	41.0%	12.7%	8

DISCUSSION

Cardiovascular events have been shown to cause depressive symptoms in up to 33% of the patients who experience them.[3] With cardiovascular disease as a leading cause of morbidity and mortality in the US it is important to address further problems it may bring forth. Although there are many medications used for the treatment of depression it is difficult for patients to find a suitable match. Many anti-depressants come with a wide array of side effects and black box warnings, making them undesirable to a large population.

An alternative treatment for depression that has been recently discussed in the literature is the use of n-3 fatty acids.[3] Omega-3 fatty acids include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They are essential fatty acids, thus can not be made by the human body but can be found in fish, algae, some plans and nut oils. Already known to be beneficial in heart disease for their decreasing effects on inflammation in the body, scientists now further look at their benefits on other psychophysiological processes.[7]

With their mild side effect profile for most patients, such as gas and diarrhea, the omega-3 fatty acids have been a great contender for randomized controlled trials to determine their efficacy. Although tolerated by many, it is important to note the more serious precautions one must take when considering supplementation. This includes blood thinning actions, possible harmful additives, and the possibility to increase fasting blood sugar levels (caution with diabetic medication).[7] Omega-3 fatty acids are available over the counter.

The omega-3 fatty acids are a critical component in the structure of the CNS membrane. With alterations in the membrane lipids comes alterations in their fluidity, leading to a change in function in receptors, enzymes and transporters. For these reasons and many more omega-3 fatty acids have been implicated to have an effect on depression. Some studies have shown patients with depression to have lower levels of fatty acids in their plasma.[7] This potential use was indicated in the study by Tajalizadekhoob et al. that demonstrated a decrease in depressive symptoms in elderly patients with diagnosed mild-moderate depression after the supplementation of n-3 fatty acids.[6]

However, limitations exist with this study by Tajalizadekhoob that hinders the expansion of the results. The population size selected was very small, including only 66 participants. The results for this study showed a NNT of 8, therefore for every 8 patients treated only one showed benefit.[6] That is, roughly only 12% showed improvement in this study. Another important limiting factor in this study is the season it was done in. The decrease in GDS-15 scores may be seasonally related since it started at the beginning of winter when depression is commonly more severe and concluded at the end of spring.

After further research of the expansion of this topic into the use of n-3 fatty acids for depression in post-cardiovascular patients, this review does not support its use. Both studies done in patients after experiencing a cardiovascular event showed no significant improvement in depressive symptoms after supplementation with n-3 fatty acids.[4,5] When Giltay and colleagues analyzed the subset group of those who took anti-depressants at baseline (Table 2), there was a minor improvement in depressive symptoms. This is a possible area for further investigation. For both of these studies sample size and duration of the study were sufficient for credibility.

Andreeva and colleagues had limitations that arose after they eliminated patients due to missing GDS scores. Because of the missing scores, by chance those still included in the trial were more likely to be retired, less likely to smoke and had somewhat lower homocysteine levels and higher n-3 PUFA concentrations. With already higher n-3 PUFA concentrations there is less room for an increased concentration to play a significant effect.[4] The major limitation with the study performed by Giltay and colleagues was that some patients did not complete the questionnaires at the 40 month follow up, all for various reasons.[5]

CONCLUSION

This review does not support the use of n-3 fatty acid supplementation for depressive symptoms in adults 40 years and older post-cardiovascular event. Not only did two studies show no benefit in depressive symptoms, but one in fact showed an increase in depressive symptoms. When Andreeva and colleagues further analyzed their studies and looked at just the experimental men group, an increase in depressive

symptoms was shown. This subset of information should be further studied to delineate the exact cause by looking at the patients included and possible confounding factors.

The potential possibilities why these studies did not show an improvement in depressive symptoms after cardiovascular event are wide and unlimited. With reasonable trial time and population selection, one must extend the evaluation of the failure of these trials to a deeper cause. One potential cause may be due to the pathophysiology behind depression associated with cardiovascular events that is still not fully understood. Perhaps in the future with a better understanding of the pathophysiology, further studies will be warranted to better treat depression in post-cardiovascular event patients.

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